NICE National Institute for Health and Care Excellence

NICE guidance

# Velmanase alfa for treating alpha-mannosidosis

Highly specialised technologies guidance
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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

# Contents

# 1 Recommendations

1.1 Velmanase alfa is recommended as an option for treating the non-neurological signs and symptoms of mild to moderate alpha-mannosidosis, only if:

- treatment is started in people under 18 years (it can be continued in people who turn 18 while on treatment)
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with velmanase alfa that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by them, their clinician, and their parents or carers.

## Why the committee made these recommendations

Alpha-mannosidosis is an ultra-rare and serious condition that severely affects the quality of life of people with the condition, and their families and carers. For this evaluation, the company asked for velmanase alfa to be considered only for people under 18 years and people who turn 18 while on treatment. This does not include everyone it is licensed for.

Clinical trial evidence suggests that velmanase alfa may lead to improvements in functions such as walking, stair climbing and lung capacity, and quality of life, for people with alpha-mannosidosis. But the size and nature of these benefits are highly uncertain because of the ultra-rare nature of the condition, which makes evidence generation difficult.

The most likely cost-effectiveness estimate for velmanase alfa is around what is considered value for money in the context of a highly specialised service. Although there are some uncertainties in the economic model, when taking into account all the evidence and the factors affecting the decision, velmanase alfa is recommended.

# 2 The condition

2.1 Alpha-mannosidosis is an ultra-rare lysosomal storage disorder caused by inheriting a faulty copy of the MAN2B1 gene from both parents. This impairs production of the enzyme alpha-mannosidase, leading to systemic accumulation of mannose-rich oligosaccharides in various tissues, especially in the central nervous system, liver and bone marrow.

2.2 The clinical presentation is associated with a wide range of impairments with varying degrees of severity. Signs and symptoms of alpha-mannosidosis can occur at a young age. The most severe forms occur during infancy (before 5 years) and are associated with rapid progression, leading to early death. More moderate forms are characterised by slower disease progression. Although people with moderate forms survive into adulthood, they have a wide range of impairments, complications and comorbidities. The impairments may include:

- facial and skeletal deformities (especially scoliosis and deformed hips and feet)
- bone deterioration, and joint and muscle weakness (leading to pain)
- mobility issues that often progress to the inability to walk unaided, or the need for a wheelchair
- hearing impairment
- speech and language difficulties
- cognitive impairment
- mental health difficulties
- reduced lung function because of an enlarged liver and spleen, and spinal abnormalities
- immunodeficiency with recurring infections (mainly respiratory and ear).

2.3 The overall prevalence of alpha-mannosidosis is estimated to be between 1 in 500,000 and 1 in 1,000,000. At the time of the evidence submission, the Society

for Mucopolysaccharide Diseases (MPS Society) estimated that there were 25 people with alpha-mannosidosis in England.

2.4 There are currently no pharmacological treatments for alpha-mannosidosis that alter the disease course. Treatments aim to manage symptoms and improve quality of life. They include walking aids, physiotherapy, infection management, ventilation support, general treatment of comorbidities, supportive measures at home and major surgical interventions (for example, ventriculoperitoneal shunts, cervical spine decompression, joint replacement). An allogeneic haematopoietic stem cell transplant from a matched sibling or matched umbilical cord donor is an option for some people when clinically indicated, but is associated with significant risks (see section 4.3).

2.5 Alpha-mannosidosis is managed in UK lysosomal storage disorder specialist centres. These centres have experience of administering enzyme replacement therapies by infusion for other related conditions.

# 3 The technology

3.1 Velmanase alfa (Lamzede, Chiesi) is an enzyme replacement therapy produced using recombinant DNA technology. It is intended to replace the natural alpha-mannosidase enzyme outside the central nervous system to help with the degradation of mannose-rich oligosaccharides. Velmanase alfa is given once a week by intravenous infusion at a dose of 1 mg/kg body weight. It has a marketing authorisation in the UK for treating 'non-neurological manifestations in patients with mild to moderate alpha-mannosidosis', but the company focused its decision problem on people under 18 years and people who turn 18 while on treatment.

3.2 The most common adverse reactions for velmanase alfa include weight gain, immune-related responses, diarrhoea, headache, arthralgia (joint pain), increased appetite and pain in the extremities. For full details of adverse reactions and contraindications, see the summary of product characteristics for velmanase alfa.

3.3 The list price of velmanase alfa is £886.61 per 10-mg vial (excluding VAT; company's evidence submission). The company has a commercial arrangement. This makes velmanase alfa available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

# 4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Chiesi, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence assessment group (EAG). After its original submission in 2018, the company resubmitted further data on separate occasions, most recently in March 2023. To date, there have been 5 committee meetings to review the evidence for velmanase alfa. In the latest submission, the company chose to restrict the population in the decision problem to people under 18 years. Although a broader population was discussed at previous committee meetings, this document summarises the committee's discussions and conclusions relating to people under 18 years. See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

## Nature of the condition

### Effect of alpha-mannosidosis on people with the condition, and their families and carers

4.1 The patient experts explained that alpha-mannosidosis affects all aspects of life for people with the condition, and their families and carers. They emphasised the all-consuming nature of the condition. The clinical and patient experts also explained that the clinical manifestations of alpha-mannosidosis can be associated with a wide range of impairments and degrees of severity. The patient experts highlighted the effects of physical symptoms, and psychological and behavioural complications, and the need for a high level of care, including repeated hospital appointments, surgical procedures and medical interventions. Social and professional life can also be compromised for people with alpha-mannosidosis, and their families and carers. A patient testimony emphasised the extent of the burden of the condition. This included difficulty in finding a job and the demoralising effect of being perceived as less capable. One patient expert explained that alpha-mannosidosis has negatively affected their

education and social interactions at school. They explained that cognitive impairments associated with the condition may also affect a person's ability to learn to drive, which reduces their independence. The committee recognised that alpha-mannosidosis is an ultra-rare condition, and the patient experts highlighted that this could mean diagnosis is delayed because it is not immediately recognised. It also recognised that many people with alpha-mannosidosis are children and young people. The committee concluded that alpha-mannosidosis is an ultra-rare, serious and debilitating condition that severely affects the lives of people with the condition, and their families and carers.

## Proposed population for velmanase alfa

4.2 Velmanase alfa has a marketing authorisation for treating non-neurological manifestations in people with mild to moderate alpha-mannosidosis (see section 3.1). The clinical experts explained that severe disease is easily distinguished by central nervous system involvement and loss of skills in the first year of life, which rapidly progresses. The velmanase alfa marketing authorisation is not restricted by age, but at the fifth committee meeting the company restricted its decision problem to people under 18 years. The committee noted that the evidence presented no longer included the full marketing authorisation population (that is, including adults), and that it could only evaluate a technology in the population for which it received clinical and economic evidence. The committee also noted less clinical benefit in adults than in children (see section 4.7) and clinical advice that treatment benefit would be expected to be greater when treatment starts early, before irreversible damage accumulates as people age. So, the committee based its evaluation on the company's revised population, focusing on people under 18 years.

## Allogeneic haematopoietic stem cell transplants

4.3 An allogeneic haematopoietic stem cell transplant (HSCT) was listed as a comparator for velmanase alfa in the scope for the evaluation. But the company did not present it as a comparator in any of its submissions. The clinical experts explained that an allogeneic HSCT is associated with significant morbidity and mortality, which increases with age. Because of this, an allogeneic HSCT is not

normally used in children over 5 years. The patient and clinical experts explained that the decision about whether to offer an allogeneic HSCT is based on a risk–benefit assessment involving the clinician, the person with alpha-mannosidosis, and their parents or carers. They further explained that the decision considers the identified mutation, the symptoms of the condition and donor availability. The committee recalled that some people would be diagnosed with mild to moderate alpha-mannosidosis when under 5 years and either a transplant or velmanase alfa could be suitable. The clinical experts explained that, for children who have central nervous system involvement that is likely to be reversible, an allogeneic HSCT would be the preferred treatment option. They further explained that people usually wait around 6 months for a transplant. The committee considered whether velmanase alfa could be used while a person is waiting for a transplant. The clinical experts explained that enzyme replacement therapies such as velmanase alfa could improve cardiac function and immune response, and reduce infections before surgery. This was based on their experience using enzyme replacement therapies in mucopolysaccharidosis 1 disease, a similar condition to alpha-mannosidosis. The company positioned velmanase alfa only for people for whom an allogeneic HSCT is unsuitable. The committee recognised that there was no data to compare velmanase alfa with an allogeneic HSCT, and very limited data for people who may use velmanase alfa while waiting for a transplant. It concluded that it would not be able to make recommendations for people for whom an allogeneic HSCT would be considered a possible treatment.

# Impact of velmanase alfa

## Clinical evidence

4.4 The committee discussed in detail the clinical evidence most relevant to the decision problem submitted by the company:

- rhLAMAN-05 (n=25) was a double-blind randomised controlled trial that assessed the efficacy and safety of velmanase alfa (n=15) compared with placebo (n=10) over 12 months. Results were reported by age group (under 18 years compared with 18 years and over) as part of the post-hoc analysis.

- rhLAMAN-08 (n=5) was a single-arm open-label study that provided data on people under 6 years who had treatment with velmanase alfa. Results were reported for changes to outcomes from baseline at 24 months for most people.
- rhLAMAN-10 (n=33; 19 children) was a single-arm open-label extension study to rhLAMAN-02, -03, -04 and -05 that provided data on treatment with velmanase alfa for up to 48 months. The study combined this with data from compassionate-use programmes and open-label studies (rhLAMAN-07 and -09) as part of an integrated analysis. Results were reported by age group in a preplanned analysis (under 18 years compared with 18 years and over) and in a post-hoc analysis (6 to 11 years, 12 to 17 years, 18 years and over).
- rhLAMAN-11 (n=33) was an update of the rhLAMAN-10 study. It included another 7 years of follow-up data from the rhLAMAN-07 and -09 studies (n=15 people). This meant that follow up for 2 people increased to 12 years. Results were reported by age group in a preplanned analysis (under 18 years, and 18 years and over).
- Interim data from the AllStripes registry study, which gave an overview of mobility impairment progression for several people (all untreated with velmanase alfa; the exact number is academic in confidence), including detailed data for 1 person from the US.
- Etoile Alpha was a real-world retrospective registry study in France. It reported biological and mobility outcomes for people having velmanase alfa. Most people in the study were included in rhLAMAN-11, but it included 4 additional children.
- The 2022 Patient and Caregiver Survey was a European and UK survey on disease progression in people aged 10 years and over. Respondents were asked to score different aspects of their condition currently, 5 years ago and 10 years ago. Descriptive results were available from 51 people, and covered visual analogue scale scores for walking and pain or discomfort, and patient and carer quality-of-life scores.
- Case reports were available for children and adults in different countries who had velmanase alfa. Descriptions of the treatment experience and outcomes were reported, but most findings were academic in confidence.

- Information and analyses requested by the US Food and Drug Administration aimed to identify multicomponent endpoints. The results were academic in confidence.

The outcomes measured in the rhLAMAN clinical studies included serum oligosaccharide levels, mobility and functional capacity, lung function, quality of life, cognition, hearing, motor proficiency, and levels of disability and pain. Other neurological outcomes were not presented and were not expected to be affected by velmanase alfa because it does not cross the blood–brain barrier. The committee acknowledged that the studies were generally well conducted and of reasonable quality. The EAG highlighted that there were uncertainties associated with the studies. It noted the lack of a control arm in rhLAMAN-10 and -11. This could have affected the interpretation of the results, especially in children, because it was not possible to adjust for the natural history of the disease at a time when major physiological changes are occurring. The EAG highlighted that most of the people included in rhLAMAN-11 were also included in other studies, including Etoile Alpha. It recommended that the committee consider rhLAMAN-11 as the primary source of evidence for long-term efficacy. The committee acknowledged that the rhLAMAN-11 evidence shared by the company directly addressed a concern around short follow-up time that it had raised previously. It noted that the results were generally similar to the rhLAMAN-10 results. But it also noted the same sample size and comparator arm concerns with rhLAMAN-11 as with rhLAMAN-10. The committee recognised these limitations were influenced by the extreme rarity of the condition. The committee concluded that the clinical-effectiveness evidence from the rhLAMAN and real-world studies was informative, but was associated with several uncertainties.

## Generalisability of the evidence to clinical practice in England

4.5 The EAG noted that, in rhLAMAN-05, more people in the velmanase alfa arm were 'compromised' at baseline than people in the placebo arm. This could have affected some outcomes, but the EAG was uncertain about whether it would favour velmanase alfa or placebo. People who were at high risk of developing reactions to velmanase alfa (those with IgE levels above 800 IU/ml) were excluded from the rhLAMAN trials. The committee felt that this might have

affected the generalisability of the safety findings. But the clinical experts stated that the people included in these trials were representative of people who would be seen in clinical practice in England. In its resubmission, the company presented clinical evidence from rhLAMAN-08 for children under 6 years. The clinical experts explained that, although there was limited evidence in this age group, there was no biological reason to expect the results to differ from those for people aged over 6 years. The committee concluded that the generalisability of the rhLAMAN clinical evidence was acceptable and the evidence was likely to be generalisable across the population.

## Serum oligosaccharide levels as a surrogate endpoint

4.6 Velmanase alfa was associated with a statistically significant reduction in serum oligosaccharide levels compared with placebo for adults and children in rhLAMAN-05, -10 and -11. The results were:

- rhLAMAN-05: the overall adjusted mean difference in relative change between velmanase alfa and placebo arms was -70.47% ($p<0.001$)
- rhLAMAN-10: the relative mean change from baseline at last observation was -57.6% ($p<0.001$) for adults and -66.6% ($p<0.001$) for children
- rhLAMAN-11: the relative mean change from baseline at last observation was -54.0% ($p<0.001$) for adults and -56.6% ($p<0.001$) for children.

Serum oligosaccharide levels were a surrogate outcome. The committee recalled that, in alpha-mannosidosis, impaired production of the alpha-mannosidase enzyme leads to increases in oligosaccharide levels, which cause the impairments in this condition. The company explained that serum oligosaccharide levels are an important biomarker that show the effect of velmanase alfa at a cellular level and are a marker of potential clinical complications of alpha-mannosidosis. The clinical experts explained that serum oligosaccharide levels are used in clinical practice to diagnose alpha-mannosidosis but, because of the lack of treatments, have not been used to assess treatment effects. The clinical experts explained that serum oligosaccharide levels could be prognostic of disease severity. They highlighted that, in other lysosomal storage disorders, substrate reduction

through enzyme replacement therapy is a way of producing important clinical benefits. But benefits vary between conditions and depend on the nature and reversibility of established damage. The EAG explained that there appeared to be only a limited relationship between serum oligosaccharide levels and clinical outcomes in the rhLAMAN trials. Also, the company did not submit any formal assessment of the surrogacy relationship using standard criteria. It did assess correlations between serum oligosaccharide levels and some outcomes in rhLAMAN-10, but these were all considered negligible or marginal. Similar assessments were not reported for rhLAMAN-05. The company shared analyses that reported the percentage of people in rhLAMAN-10 who had improvements in both serum oligosaccharides and 1 of 3 key outcomes. The EAG commented that the analyses showed some correlation, but that it was not strong. In its opinion, changes in serum oligosaccharides cannot reliably predict clinical response. The EAG also noted that not all outcomes were included in the analyses, and that correlation between serum oligosaccharides and the Childhood Health Assessment Questionnaire disability index (CHAQ-DI) and the EQ-5D-5L was not reported. The committee concluded that the results provided biochemical evidence that velmanase alfa has an effect, but it was not able to infer the nature or size of the clinical benefits from these results.

## Mobility, functional capacity and quality of life

4.7 In rhLAMAN-05, there were no statistically significant differences between velmanase alfa and placebo at 12 months in:

- mobility and functional capacity (3-minute stair climb test [co-primary endpoint], 6-minute walk test, forced vital capacity)
- quality of life (CHAQ-DI, EQ-5D-5L).

The EAG was unclear whether the trial met its objective of showing clinical efficacy in functional endpoints. In rhLAMAN-11, age-adjusted and age-unadjusted results were available for some outcomes. The differences in outcomes compared with baseline at the last observation were:

- 3-minute stair climb test: +18.2% (p=0.01) for children, -1.3% (p=0.8) for

adults

- forced vital capacity: +78.3% for children, -3.7% for adults (p values not reported)
- age-adjusted forced vital capacity (% predicted): +17.9% ($p<0.01$) for children, -8.4% ($p\geq0.05$) for adults
- 6-minute walk test: +11.3% ($p<0.05$) for children, -6.6% ($p<0.05$) for adults
- age-adjusted 6-minute walk test (% predicted): +2.7% for children, -5.1% for adults (p values not reported)
- EQ-5D-5L: +12.4% for children, +4.7% for adults (p values not reported).

The committee noted that velmanase alfa appeared to be more effective, and that the results were more statistically significant, in children compared with adults. It also noted that the outcomes were marginally increased or the same as in rhLAMAN-10, apart from the change in EQ-5D-5L score which reduced from +0.08 in children in rhLAMAN-10 to +0.05 in rhLAMAN-11. The committee discussed how to interpret the clinical-effectiveness results. It noted that the age-adjusted results for the 6-minute walk test and forced vital capacity showed smaller increases from baseline than the age-unadjusted results. This meant that some of the changes in absolute values are related to physiological changes with age. During the fifth committee meeting, the patient and clinical experts explained that in children, outcomes can be influenced by factors other than treatment effect and age-related changes. They explained that increased familiarity with tests as they are repeated could lead to improved results, while waning of enthusiasm as the test is repeated could produce the opposite effect. The committee noted that the size of the observed benefits was small, but recalled the company identifying that improved outcomes were clinically relevant based on minimally important differences. The clinical experts also explained that small improvements would be important to people with the condition. So, the committee noted that the benefits would likely translate into meaningful improvements for people with alpha-mannosidosis, especially if disease stabilisation is possible in this progressive disease. The committee recognised that the small population size likely influenced the uncertainty of the evidence (for example, statistical significance), but it would not

necessarily be expected to have affected the size of the benefits. It noted the clear difference in treatment benefits for children compared with adults. The committee concluded that the evidence suggested that velmanase alfa is a promising treatment, but that there was insufficient evidence to establish the extent of the clinical benefits.

## Infections

4.8 In rhLAMAN-05, there was a statistically significant improvement in serum IgG levels with velmanase alfa (adjusted mean difference compared with placebo: 3.47 g/litre, $p<0.0001$). Of the people in rhLAMAN-05 with low levels of IgG at baseline (n=9/25, of which 5 were in the velmanase alfa arm), 60% (n=3/5) in the velmanase alfa arm had normal IgG levels after 12 months and 40% (n=2/5) had improved levels; no people in the placebo arm had improved levels. The clinical experts stated that these results were striking, and that IgG might be a relevant surrogate marker for immune function because of the nature of the immune problems associated with alpha-mannosidosis. A post-hoc analysis of antibiotic use in the low-serum IgG group showed that people in the velmanase alfa arm used fewer antibiotics than people in the placebo arm. In response to consultation, the company explained that rhLAMAN-05 showed that after 1 month, the rate of infection per infected patient was 1.5 in the placebo arm compared with 0 in the velmanase alfa arm. Serum IgG levels were also reported in rhLAMAN-10 and -11. They showed a 51.7% increase in rhLAMAN-10 and a 48.2% increase in rhLAMAN-11 in people under 18 years. An analysis of carers' reports of infection rates supported a reduced number of infections associated with velmanase alfa in rhLAMAN-10. The company interpreted this data as showing likely improvements in infection rates. The committee noted comments from the patient experts and testimonies from people who had had treatment with velmanase alfa. These highlighted the effect of recurrent infections associated with alpha-mannosidosis, and reported that there were fewer infections with velmanase alfa treatment. The committee concluded that velmanase alfa appears to have immunological benefits by reducing infections, but that the evidence on this is limited and uncertain.

## Adverse events

4.9 The proportion of people having velmanase alfa who had any adverse event in rhLAMAN-05 and -10 was high (88% to 100%), but most events were reported as being mild or moderate. The most frequent adverse events with velmanase alfa were infection and infestation (86.7% of people in rhLAMAN-05 and 72.7% in rhLAMAN-10). The EAG explained that the safety of treatment over a lifetime is unknown. The committee concluded that the tolerability profile of velmanase alfa was likely to be acceptable.

# Cost to the NHS and value for money

## Company's economic model

4.10 The company presented an economic analysis based on a Markov model, in which people could move through 4 primary health states according to their mobility (walking unassisted, walking with assistance, wheelchair dependent, severe immobility) or enter the absorbing death state. People could also have severe infections or major surgery. The model was based on a cohort of people under 18 years, based on the company's restricted population. The committee questioned the appropriateness of the model structure and whether important aspects of alpha-mannosidosis were captured. It considered that mobility would be expected to capture many of the important aspects of alpha-mannosidosis for people. But it noted that within each health state, functional improvements, and reductions in minor infections and surgery, would not be captured. The company said that the model might also not capture improvements in hearing impairment, non-joint pain, fine motor deficits, fatigue, mental health, cognitive function, psychiatric events and independence. The committee concluded that while other measures of disease progression, such as lung function, could be an option for defining the model structure, the overall model structure was adequate for decision making.

## Sources of data in the model

4.11 Most of the parameters used to inform the model were assumptions based on expert elicitation panels, or from interviews with key opinion leaders. This was because clinically important aspects (such as rate of progression of mobility impairment, severe infections and need for surgical intervention) were not captured in the rhLAMAN trials. The parameters derived from the clinical study observations were limited to the starting health state of the population and the rate of stopping treatment because of lack of efficacy. But the company explained that rhLAMAN-11 data supports the delay in disease progression (see section 4.12). The committee was concerned that so few parameters in the model were directly informed by data from the clinical trials despite more data becoming available. It recognised that the expert elicitation panel was based on a formal elicitation process using well-established methods, although the EAG explained that the key opinion leader interviews had greater limitations. The committee was reassured that experts and key opinion leaders from the UK were enrolled in these studies, so their experiences were likely to represent UK clinical practice. But the company did not repeat the expert elicitation panel to consider the longer-term evidence available from Etoile Alpha and rhLAMAN-11 as part of the resubmission. This increased the uncertainty in the model assumptions. The committee understood the reason for the lack of clinical data. But it concluded that the extensive use of elicited data and expert opinion, and the lack of observed evidence to inform the model, were significant limitations in the economic analysis. It also concluded that the size and direction of any errors or bias were unknown.

## Benefits of velmanase alfa in the model

4.12 The company's revised paediatric model captured different aspects of the expected benefits of velmanase alfa. Velmanase alfa was assumed to:

- delay disease progression by 6 years compared with best supportive care, supported by rhLAMAN-11 and Etoile Alpha results
- improve some peoples' mobility from baseline (that is, people in the walking with assistance and wheelchair-dependent health states could move to better health states in the model), based on the expert elicitation panel

- reduce the mortality, complications and recovery time associated with severe infections and major operations by 50% compared with best supportive care.

The company no longer assumed that velmanase alfa also extended the time in each subsequent health state after progression. It explained that this was to simplify the model assumptions to reduce reliance on expert opinion, and in response to the EAG's concern, to avoid potential double-counting of the benefits of velmanase alfa. The committee recognised these efforts but still noted that most model assumptions were based on expert opinions, rather than directly informed by clinical study evidence. The company explained that longer delay in disease progression was supported by the mean treatment duration in rhLAMAN-11 being close to 6 years (the exact value is academic in confidence and cannot be reported here). The EAG explained that using mean treatment duration was misleading and that a median treatment duration of 4.5 years was a better measure. It noted that data for individual patients submitted by the company showed that a few people's condition got worse while on velmanase alfa based on CHAQ-DI score. So, not all people may benefit from a long-term delay in disease progression. The committee acknowledged the challenges in estimating the rate of progression through the model but agreed with the EAG that median treatment duration was a better estimate because the distribution of treatment duration data was skewed. It concluded that assuming 4 years of delayed disease progression followed by an extended time in health states based on the original expert elicitation was preferrable for decision making, while accounting for uncertainty in the evidence. The committee emphasised the high level of uncertainty associated with the modelled delayed disease progression, which could have had a substantial effect on the incremental cost-effectiveness ratio (ICER).

## Benefits of best supportive care in the model

4.13 The assumed improvements from baseline (that is, that people having velmanase alfa could improve their health state whereas those having best supportive care could not) contradicted what was seen in rhLAMAN-05. In this trial, the same proportion of people improved from walking with assistance to walking unassisted in the velmanase alfa and placebo arms. The company explained that

this assumption reflected clinical experts' views because it was not plausible that people having best supportive care would improve in the long term without surgery. Improvement in physiological measurements would be expected with best supportive care in children because of growth and development (see section 4.7). The clinical experts explained that although mobility outcomes for best supportive care might improve with age, these would not necessarily be because of disease improvements. The committee recognised the uncertainty in the improvements modelled in the company's base case. But it thought that the likelihood of improving mobility in the model should have been consistent with the observed trial data. It did not consider it reasonable to assume people on best supportive care would see no mobility improvements. The EAG presented a scenario analysis that assumed people on best supportive care had a 10% chance of improving mobility in the first year, based on key opinion leader input. The committee concluded that the model should allow people on best supportive care to have a 10% chance of improving mobility in the first year.

## Starting distribution among health states in the model

4.14 The company's model allows the user to define the proportion of people in the model who start in each health state. At the fourth committee meeting, the committee concluded that the EAG's approach of using the walking health state distribution from rhLAMAN-10 should be used for decision making. At the fifth committee meeting, the company used rhLAMAN-10 data but assumed that people who are already in a wheelchair would not start treatment. So, the company assigned people who were in a wheelchair at baseline to the walking with assistance health state. This resulted in a starting distribution of 75% of people in the walking unaided health state and 25% of people in the walking with assistance health state. The EAG noted that if people who depend on a wheelchair at baseline would not have treatment, they should be excluded from calculations, rather than combined with the walking with assistance group as in the company's calculations. This resulted in a starting distribution of 86% of people in the walking unaided health state and 14% of people in the walking with assistance health state. The clinical experts explained that there are very few children, if any, who depend on a wheelchair when diagnosed. They added that even if there were such children, they could still benefit from treatment with velmanase alfa (see section 4.2). A patient expert also added that all children

known to the MPS Society were mobile and did not need assistance with walking when diagnosed. The committee considered that it was highly unlikely for children to need a wheelchair at the time they would be offered velmanase alfa. So, it preferred the EAG's starting distribution for health states, which excluded people who depended on a wheelchair at baseline.

## Starting age of people having treatment in the model

4.15 The company's revised base case at the fifth committee meeting assumed that people in the model started treatment at age 6. This was to reflect the company's revised population (people under 18 years, see section 4.2). The company cited published evidence reporting a mean age at diagnosis of 7 years, but noted this was outdated, and mean age of diagnosis in the UK is plausibly lower. This is because diagnostic testing is improving rapidly with the introduction of next-generation sequencing and newer gene panels, plus the possibility of newborn screening in the future. At a previous committee meeting, one clinical expert explained that there are 3 routes to diagnosis in younger children. These include:

- diagnosis on clinical grounds when there is a high burden of clinical symptoms and rapid progression suggestive of severe disease (the person would not be eligible for treatment with velmanase alfa)
- detection in children under 6 years when there is clinical suspicion, but diagnosis needs confirmation by genetic and biochemical testing
- diagnosis in children who are asymptomatic and have siblings with alpha-mannosidosis, which can only be done by laboratory investigation.

The NHS England representative confirmed that these were the appropriate routes of diagnosis. At the fifth committee meeting, the clinical experts agreed that the use of genetic screening was expanding as outlined by the company, leading to the identification of people with alpha-mannosidosis who otherwise would not have been diagnosed. The clinical experts added that this would lead to a more variable age at diagnosis with some people over 6 years being diagnosed. A patient expert explained that all children known to the MPS Society were diagnosed at a mean age of 4 years with a range of 2 to 5 years. The EAG explained that the company's assumption of

starting treatment at 6 years was plausible but subject to uncertainty. So, it provided a scenario analysis assuming starting treatment at 8 years. The committee agreed that the trend in the UK is towards diagnosis at earlier ages, but acknowledged that some older children could still be diagnosed. It concluded that the effect of this on the average age of diagnosis would be small and reduce over time. So, the committee agreed that it is appropriate to assume a starting age of 6 years.

## Quality of life and additional utility gain associated with velmanase alfa

4.16 The company model assumed that people would have a utility gain because of velmanase alfa's effects on mobility, major infections and need for surgery. The model also assumed people would have an additional utility benefit throughout treatment to account for many aspects of alpha-mannosidosis that were not captured in the model. These included:

- improving lung function
- reducing rates of minor infections and minor surgery
- reducing rates of psychiatric problems, and improving cognition and mental health
- improving hearing, upper extremity and fine motor deficits
- reducing pain and fatigue
- reducing ventilation dependency
- improvements in the ambulatory health states (walking unassisted, walking with assistance)
- the possibility that some further benefits of velmanase alfa would appear after several years of treatment.

The company also noted that its revised model assumed no extended time in health states, so utility benefit as people progress would be underestimated.

The committee recognised that, beyond the modelled health states for mobility and infection, there may be additional benefits from velmanase alfa not captured in the model. But it agreed that the exact utility gain was uncertain. At the fifth committee meeting, the company updated the utility benefit for children to 0.18. This was based on EQ-5D values mapped from the forced vital capacity test results in rhLAMAN-10. It used assumptions from NICEs highly specialised technologies guidance on elosulfase alfa for treating mucopolysaccharidosis type 4A. In this, a utility gain had been accepted that was linked to improvements in forced vital capacity (0.2 utility per 1 litre gain). This was to account for the association between improvements in this parameter and increased quality of life and survival. The clinical experts explained that mucopolysaccharidosis 4A is a similar condition to alpha-mannosidosis in that it is a heterogeneous lysosomal storage disease that has a large effect on people's quality of life. The company explained that long-term respiratory benefit in rhLAMAN-11 was higher than in rhLAMAN-10 (+1.2 litres compared with +0.9 litres), so an additional utility benefit of 0.18 was conservative. The committee noted that the additional utility gain mapped by the company lacked face validity, because it was considerably larger than the EQ-5D benefit directly observed for children in rhLAMAN-10 and rhLAMAN-11 (+0.08 and +0.05, respectively). The committee was aware of the potential issues with using the EQ-5D to assess quality of life in children. It also noted that the forced vital capacity test results used for mapping had not been adjusted for age and that the positive association between forced vital capacity and EQ-5D score was only seen in adults. Forced vital capacity is related to physiological growth, and age-adjusted benefits in forced vital capacity were much lower than unadjusted benefits (see section 4.7). So, any gain in utility may have been overestimated. The committee also noted that the company's updated additional utility gain from treatment with velmanase alfa (that captured effects beyond its effect on mobility) was considerably larger than the utility gain from moving between mobility-based health states. Also, when adding a 0.18 utility gain to the existing value for the walking with assistance health state, people whose disease responded to velmanase alfa had a utility value close to that of the general population. This did not align with the clinical evidence or submissions from the patient and clinical experts. The committee concluded that it preferred a utility benefit of 0.05 from the EQ-5D utility gains directly observed in rhLAMAN-11. The committee recognised that the

model may still not include benefits from velmanase alfa. So, accounting for the uncaptured benefits, the committee agreed that a 0.1 utility gain for children should be used for decision making.

## Resolved issues

4.17 During the fifth meeting, the committee focused on the company's latest submission and submissions from stakeholders. The committee felt that several issues that were previously discussed had been resolved because these issues were addressed in the latest company base case (see table 1). But the committee considered scenario analyses which explored the resolved issues.

**Table 1 Previously resolved key issues**

| | |
|---|---|
| **Health state utility values** | • The committee stated a preference for utility values from rhLAMAN trials rather than from the MPS Society survey.<br>• The committee concluded that both sources of utility values were highly uncertain. But the MPS Society survey values were based on a smaller sample size and estimated implausibly high utility values for the walking unassisted health state. |
| **Caregiver disutility** | • Carer utilities as included in the company base case were considered and accepted by the committee. |
| **Ventilation costs** | • The committee concluded that the assumption that people who had velmanase alfa first and stopped treatment (switching to best supportive care) would need 50% less ventilation assistance than people having best supportive care throughout was not appropriate.<br>• The committee preferred to remove the assumption of continuing benefit of velmanase alfa on ventilation assistance. |

| | |
|---|---|
| **Home-infusion costs** | • The committee concluded that including costs of once-weekly home infusion for people having velmanase alfa was appropriate based on patient expert testimony. |
| **Stopping rules** | • The committee accepted the company's use of stopping rules in its base case to reflect that treatment would stop for people who do not benefit, have life-limiting conditions, or cannot tolerate the treatment or adhere to monitoring. |
| **Discounting rate for costs and health effects** | • The committee concluded that velmanase alfa does not meet NICE's criteria for applying a discount rate of 1.5% because the technology could not return people to full or near-full health and evidence was not clear that long-term health benefits were highly likely to be achieved.<br>• The committee concluded that a discount rate of 3.5% should have been applied for costs and health effects. |
| **Costs in the model** | • The committee concluded that it was appropriate to calculate velmanase alfa costs using a distribution of people's weights from data obtained by the Medical Research Council and to adjust health state costs for inflation.<br>• The committee concluded that the effect of assuming treatment stopped because of a lack of efficacy in the middle of the first year was small. |

## Cost-effectiveness results

4.18 The company's final base case produced an ICER for velmanase alfa of £61,396 per quality-adjusted life year (QALY) gained in children. The EAG's base case produced an alternative ICER of £112,623 per QALY gained in children. The EAG's base case differed from the company base case because of the following assumptions:

- 3 years of delayed disease progression followed by an extended time in

health states for children having velmanase alfa

- an additional utility gain (beyond the utility gain related to improvements in mobility health states) of 0.10 for children having velmanase alfa
- a starting population distribution in modelled health states of 86% for walking unassisted and 14% for walking with assistance.

The company and the EAG presented scenario analyses related to:

- improvements in mobility for children having best supportive care
- the duration of halted disease progression associated with velmanase alfa
- the starting population distribution among modelled health states
- the treatment starting age for children
- the additional utility benefit for children having velmanase alfa.

The committee recognised the company's efforts to accommodate its preferences into the latest company base case, and for providing new evidence when appropriate for assumptions that differed from previous committee preferences. Taking into account its conclusions on the key assumptions discussed at the fifth meeting (in addition to the resolved key issues in section 4.17), the committee considered that its preferred base case was:

- 10% chance of improvement in mobility in the first year for children having best supportive care (see section 4.13)
- delayed disease progression for 4 years for children whose condition responded to velmanase alfa, followed by an extended time in health states (see section 4.12)
- a starting population distribution among modelled health states of 86% for walking unassisted and 14% for walking with assistance (see section 4.14)
- a starting age for children in the model of 6 years (see section 4.15)
- an additional utility gain of 0.1 for children having velmanase alfa (see

section 4.16).

Because of the efforts of the company and EAG, the committee was able to determine a most plausible ICER with more confidence than at the last meeting. But the cost-effectiveness estimates were still associated with high uncertainty because of the extensive use of elicited data and expert opinion (see section 4.11). The committee concluded that, based on its preferred assumptions, the most plausible ICER was £103,600 per QALY gained in children.

## Application of QALY weighting

4.19 The committee understood that NICE's health technology evaluations manual specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the incremental QALY gains associated with velmanase alfa and highlighted that these were substantially below 10 in the company's final base case. The committee concluded that there was no evidence to suggest that velmanase alfa would meet the criteria for applying a QALY weight.

## Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.20 The committee discussed the effect of velmanase alfa beyond its direct health benefits. It understood from the patient and clinical experts that all aspects of life for people with alpha-mannosidosis, and their families and carers, are affected by the condition. It noted that people with the condition need a high level of care, and that educational, professional and social life could be compromised for them

and their families and carers. It also noted that alpha-mannosidosis is managed in established lysosomal storage disorder specialist centres. So, no additional infrastructure or staff training would be needed to manage use of velmanase alfa in England.

# Other factors

## Innovation

4.21 The committee discussed the innovative nature of velmanase alfa, noting that it is the first pharmacological disease-modifying therapy for alpha-mannosidosis and that there is significant unmet need for it. The company considered that velmanase alfa is a step-change in managing alpha-mannosidosis. This was because of its potential to change the natural course of the disease by improving mobility or delaying disease progression. The committee concluded that velmanase alfa is innovative.

## Equalities

4.22 The committee recognised that alpha-mannosidosis can have a substantial effect on people's lives, and many people with alpha-mannosidosis are considered to be disabled in the Equality Act 2010. It discussed whether the evaluation might disadvantage disabled people. It felt that the effect of the disability associated with this condition and the benefits of the technology had been fully captured in the evidence, economic modelling and committee considerations. The committee highlighted that it had fully considered all available evidence including case studies, clinical expert opinion and patient testimonies. It concluded that it had taken into account the disability associated with this condition when developing its recommendations. At the fourth committee meeting, the committee considered that people with alpha-mannosidosis may have cognitive impairments that make completing quality-of-life questionnaires challenging. It acknowledged that this increased the uncertainty in the results and noted the small number of people in the company's trials. But it agreed that this issue had been considered in its preferred utility benefit for velmanase alfa, which was above that recorded

using EQ-5D questionnaires in rhLAMAN-10 and rhLAMAN-11 (see section 4.16). The committee carefully considered whether this topic warranted any additional considerations and reasonable adjustments over and above what is normally afforded to topics in the highly specialised technologies programme because of equalities issues. It also considered the comments on these factors received during consultation and at resubmission. It concluded that all relevant factors had already been taken into account, and that no additional considerations were needed regarding equalities concerns.

## Evidence generation

4.23 The committee noted that the evidence presented by the company focused on a narrower population than the marketing authorisation (see section 4.2). The committee discussed whether any consideration should have been made to reflect the fact that the population for this technology focuses on children. It was aware that alpha-mannosidosis is a serious condition that begins in infancy. It considered that the clinical evidence and economic model, and its understanding of the nature of the condition, reflected the fact that children are affected by the condition. The committee also recalled that alpha-mannosidosis is ultra-rare, even in the context of highly specialised technologies evaluations. It recognised that people with ultra-rare conditions can otherwise be disadvantaged, because of the challenges in developing medicines for these conditions and collecting appropriate evidence. It considered that it was appropriate to take into account the very small population size in its decision making because alpha-mannosidosis is considerably rarer than most conditions seen in highly specialised technologies evaluations. The committee considered whether difficulties with evidence generation could warrant it applying greater flexibility to uncertainty, in line with NICE's health technology evaluations manual. The manual states that the committee may apply greater flexibility when there are difficulties with evidence generation for:

- rare diseases
- technologies for a population that is predominantly children (under 18 years)
- innovative and complex technologies.

It considered this alongside the full range of factors affecting decision making in the highly specialised technologies programme (including the nature of the condition, clinical evidence generation, value for money and impact of the technology beyond direct health benefits). The committee concluded that greater flexibility could be applied because velmanase alfa and alpha-mannosidosis covered all 3 areas for difficulties with evidence generation specified in the manual.

# Conclusion

4.24 The committee acknowledged that alpha-mannosidosis is an ultra-rare condition that causes a wide variety of symptoms and impairments. It also agreed that it has a serious and substantial effect on the quality of life of people with the condition, and their families and carers. It was aware that small increases in clinical outcomes can translate to substantial improvements for people with alpha-mannosidosis. The committee noted that the clinical evidence suggested that velmanase alfa may provide clinical benefits. But it considered that these clinical benefits were highly uncertain because of important limitations in the nature and extent of the evidence, and the size of the improvements seen in the clinical trials. The committee considered that the most plausible ICER to inform decision making was £103,600 per QALY gained. It also noted that velmanase alfa did not meet the criteria for QALY weighting to be applied, and that important uncertainties in the economic model remained. But the committee accepted that it was appropriate to take into account the difficulties with evidence generation and apply greater flexibility to uncertainty (see section 4.23). Overall, the committee concluded that the greater flexibility adopted meant velmanase alfa would provide value for money and could be recommended for routine commissioning. So, the committee recommended velmanase alfa as an option for treating alpha-mannosidosis in children.

# 5 Implementation

5.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has alpha-mannosidosis and the doctor responsible for their care thinks that velmanase alfa is the right treatment, it should be available for use, in line with NICE's recommendations.

# 6 Evaluation committee members and NICE project team

## Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## Chair

**Peter Jackson**
Chair, highly specialised technologies evaluation committee

## NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of health technology analysts (who act as technical leads for the evaluation), technical advisers and project managers.

**Aminata Thiam, Sohaib Ashraf, Emma Douch, Owen Swales**
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# Accreditation